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14. ABSTRACT

There is an expectation that repeated daily exposures to normobaric hypoxia (NH) will induce ventilatory acclimatization (VEacc) and be effective for lessening acute mountain sickness (AMS) and the exercise performance decrement during subsequent hypobaric hypoxia (HH) exposure. However, this notion has not been tested objectively. Healthy, unacclimatized sea level (SL) residents slept for 7.5 hrs each night for 7 consecutive nights in hypoxia rooms under either NH (n=14, 24±5 yr; mean±SD) or "sham" (n=9, 25±6 yr) conditions. The ambient %O2 for the NH group was progressively reduced by 0.3%O2 (150 meters equivalent) each night from 16.2%O2 (2200 m eq) on the 1st night to 14.4%O2 (3100 m eq) on the 7th night, while that for the ventilatory and exercise-matched sham group remained at 20.9%O2. Beginning 25 hrs post-sham or NH treatment all ascended and lived for 5 days at HH (4300 m). Partial pressure of end-tidal CO2 (PetCO2), oxygen saturation (SaO2), AMS, and heart rate (HR) were measured repeatedly during daytime rest, sleep or exercise (11.3 km treadmill time trial (TT)). From pre-to post-treatment at SL, resting PetCO2 decreased ($p<0.01$) for the NH group (39±2 to 35±3 mmHg) but not for the sham group (39±2 to 38±3 mmHg). Throughout

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Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude

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Fulco CS, Muza SR, Beidleman BA, Demes R, Staab JE, Jones JE, Cymerman A. Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude. *Am J Physiol Regul Integr Comp Physiol* 300: R428–R436, 2011. First published December 1, 2010; doi:10.1152/ajpregu.00633.2010.—There is an expectation that repeated daily exposures to normobaric hypoxia (NH) will induce ventilatory acclimatization and lessen acute mountain sickness (AMS) and the exercise performance decrement during subsequent hypobaric hypoxia (HH) exposure. However, this notion has not been tested objectively. Healthy, unacclimatized sea-level (SL) residents slept for 7.5 h each night for 7 consecutive nights in hypoxia rooms under NH [n = 14, 24 ± 5 (SD) yr] or "sham" (n = 9, 25 ± 6 yr) conditions. The ambient percent O_2 for the NH group was progressively reduced by 0.3% [150 m equivalent (equiv)] each night from 16.2% (2,200 m equiv) on *night 1* to 14.4% (3,100 m equiv) on *night 7*, while that for the ventilatory- and exercise-matched sham group remained at 20.9%. Beginning at 25 h after sham or NH treatment, all subjects ascended and lived for 5 days at HH (4,300 m). End-tidal P_{CO_2}, O_2 saturation (Sa_{O_2}), AMS, and heart rate were measured repeatedly during daytime rest, sleep, or exercise (11.3-km treadmill time trial). From pre- to posttreatment at SL, resting end-tidal P_{CO_2} decreased ($P < 0.01$) for the NH (from 39 ± 3 to 35 ± 3 mmHg), but not for the sham (from 39 ± 2 to 38 ± 3 mmHg), group. Throughout HH, only sleep Sa_{O_2} was higher (80 ± 1 vs. 76 ± 1%, $P < 0.05$) and only AMS upon awakening was lower (0.34 ± 0.12 vs. 0.83 ± 0.14, $P < 0.02$) in the NH than the sham group; no other between-group rest, sleep, or exercise differences were observed at HH. These results indicate that the ventilatory acclimatization induced by NH sleep was primarily expressed during HH sleep. Under HH conditions, the higher sleep Sa_{O_2} may have contributed to a lessening of AMS upon awakening but had no impact on AMS or exercise performance for the remainder of each day.

ventilatory acclimatization; physical performance; hypobaric hypoxia; arterial oxygen saturation

ALTITUDE ACCLIMATIZATION RESULTS from numerous interrelated physiological adjustments that compensate for hypoxemia, with augmented ventilation being one of the most important and consistently reported (17, 18, 22, 28). Ventilatory acclimatization (VEacc) can be characterized by the progressive decrease in the end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) that leads to an increase in arterial O_2 saturation (Sa_{O_2}) during the first several days of moderate- to high-altitude residence [hypobaric hypoxia (HH), reduced barometric pressure (P_B) and 20.9% O_2] (7, 28). The enhanced oxygenation is closely linked with reduced acute mountain sickness (AMS) and improved exercise performance during HH residence (1, 11, 12, 14). Some studies show that VEacc can also be induced by 1–4 h of HH exposure repeated daily at altitudes of 4,300–4,500 m in as few as 7 days and that this method of HH exposure is as beneficial as continuous HH residence for reducing AMS and improving exercise performance (2, 4, 18).

A comparable degree of VEacc can similarly be induced as a result of repeated daily normobaric hypoxia (NH) exposures (maintained P_B and <20.9% O_2) using many different combinations of hypoxia duration, severity, and frequency (22). What has not been established, however, is whether NH exposure is any more effective than no treatment for mitigating undesirable outcomes such as AMS or the initial large impairment in exercise performance during subsequent HH residence (22). The only controlled, experimental studies reporting that AMS, exercise performance, and other physiological outcomes were affected favorably relative to no treatment utilized HH treatment prior to HH residence (2–4, 18) or NH treatment prior to NH residence (17, 22). Until two other studies were published recently (5, 27), no data existed to determine directly whether NH treatment would be more beneficial than no treatment during subsequent HH residence.

In one of these studies, our group (5) showed that, after induction of VEacc with 21 h of NH treatment (P_{O_2} = 90 mmHg for 2 h/day and 110 mmHg for 1 h/day) over 7 consecutive days, the impairment of time-trial (TT) exercise performance assessed within a few hours after rapid ascent to HH (446 mmHg) was not attenuated. The other study (27), which used 14–18 h of NH treatment (12–16% O_2 for 70–90 min/day, 3 days/wk, for 4 wk), along with an overnight stay at 3,611 m, reported no differences in arterial blood gases or AMS compared with no NH treatment during subsequent HH residence at 4,559 m. One interpretation suggested for the lack of effectiveness was a loss of VEacc prior to HH residence (5) that resulted from being at sea level (SL) without NH treatment for much longer than the ≤24 h used during previous successful HH treatment studies (2, 4). However, this interpretation is inconsistent with the results of at least one study (17) that reported that VEacc remained evident when assessed under NH ambient conditions 1 mo after the NH treatment ended. An alternative interpretation for the lack of effectiveness could then be that NH treatment does not provide any additional ventilatory, AMS symptom, or exercise performance benefit during subsequent HH residence.

The main purpose of the current study was to assess the effectiveness of NH treatment per se by minimizing the time between the end of NH treatment and the beginning of HH

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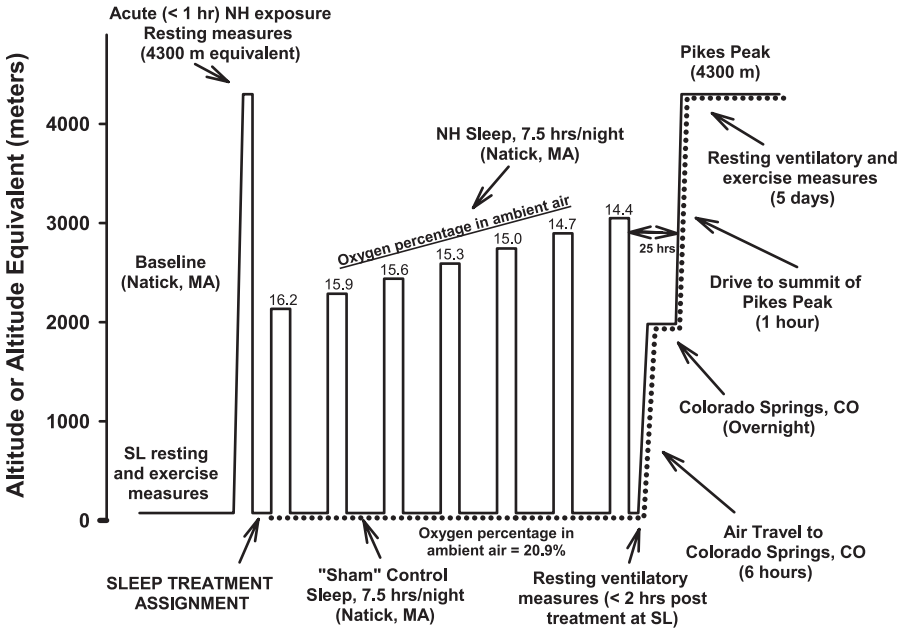

Fig. 1. Experimental design. Resting measures [i.e., ventilation, arterial O_2 saturation (Sa_{O_2}), heart rate (HR), venous blood] and exercise determinations of peak O_2 uptake ($\dot{V}O_{2peak}$) and endurance performance (steady state at 45% of $\dot{V}O_{2peak}$ and a 7-mile time trial) were obtained during the ~2-wk sea-level (SL) baseline phase. Also during the baseline phase, resting measures were obtained on all volunteers during an acute <1-h exposure to normobaric hypoxia [NH (12.2% O_2, 4,300 m equivalent)]. After being assigned to the NH (solid line) or the "sham" control sleep (dotted line) treatment group, volunteers slept for 7 consecutive nights in one of two adjacent and identical 2.4 × 3.0 × 2.3 m rooms; volunteers were blind to the treatment they received. Before (at ~2200) and after (at ~0530) each night of sleep, acute mountain sickness (AMS) was assessed, and Sa_{O_2} and HR were obtained. Motion, Sa_{O_2}, and HR were obtained continuously during sleep. Within 2 h of awakening after *night 7*, posttreatment resting measures were obtained at SL. All volunteers were then flown within several hours to Colorado Springs, CO [2,100 m, barometric pressure (P_B) ~600 mmHg], where they resided until ~0600 the next morning. At ~0700, all arrived by car at the summit of Pikes Peak (4,300 m).

residence. We included in the shortened time interval both airplane travel and an overnight stopover at a moderate altitude of 2,100 m to provide a more realistic scenario that would likely be used by individuals for work or recreational activities. The subsequent HH residence was also lengthened to 5 days to determine whether prior NH treatment would alter the rate of acclimatization.

Our approach was to subject individuals to moderate levels of NH during sleep, so that the daily "dose" would be as long as practically possible without interfering with daytime activities and also not so severe as to disrupt sleep. This approach also minimized the NH stimulus "down time" between consecutive treatment exposures (22). To that end, treatment involved sleeping for 7.5 h each night for 7 consecutive nights in a room under ambient NH conditions that simulated progressively increasing altitudes ranging from 2,200 to 3,100 m. The total NH treatment duration was therefore 52.5 h, which was nearly twice as long as the minimal total HH treatment duration previously determined to be beneficial during subsequent HH residence (5) and approximately three times longer than the two recent NH treatment-to-HH residence studies described above (5, 27). We hypothesized that VEacc induced by NH treatment would be evident, AMS susceptibility would be reduced, and TT exercise performance would be improved compared with a no-treatment control ("sham") group during the first 5 days of residence at a terrestrial elevation of 4,300 m.

METHODS

Volunteers

Twenty-three unacclimatized SL residents (20 men and 3 women) volunteered to participate. None was born at altitudes >2,100 m, and all had been living at low altitudes (<1,000 m) for ≥3 mo prior to the start of the study. All provided verbal and written consents after being fully informed of the nature of the study and its possible risks and benefits. The study was approved by the Institutional Review Boards of the US Army Research Institute of Environmental Medicine (USARIEM) and the Human Research Protection Office, US Army Medical Research and Materiel Command.

Experimental Design Overview

Each volunteer participated in three distinct phases at two different test facilities over a total period of 3–4 wk in the following order (Fig. 1): *1*) a baseline SL assessment phase at USARIEM, Natick, MA (2 wk, 50 m, P_B ~756 ± 2 mmHg), *2*) a 7-night sleep-treatment phase in Natick, MA, and *3*) a 5-day HH phase at the summit of Pikes Peak, Colorado Springs, CO (4,300 m, P_B ~459 mmHg). During testing in all phases, the temperature was maintained at 21 ± 3°C.

After SL baseline testing was completed but before the sleep-treatment phase began, "squads" of two to four volunteers were randomly assigned to a NH sleep-treatment group (n = 14) or a sham sleep-treatment control group (n = 9). Assignment of each volunteer to each squad was based on their availability to travel to Colorado Springs on predetermined dates. All volunteers were blind to their sleep-treatment assignment until the end of the study. No differences between groups existed for age, weight, height, $P_{ET_{CO_2}}$ during rest under SL and NH (1 h of exposure to 93 mmHg ambient P_{O_2}) conditions, and peak and TT exercise performance (Table 1).[1]

During the sleep-treatment phase, a squad reported each night at 2200 to a large room containing two identical 2.4 m wide × 3.0 m

[1] At 2 days after the sleep-treatment phase began, a volunteer in the sham group broke a toe (unrelated to the study) and could not participate in the remaining exercise tests but did participate in all other assessments and activities. Only his resting and sleep data were included in the final analyses.

Table 1. *Volunteer characteristics*

	NH Treatment (n = 14)	Sham Treatment (n = 9)
Age, yr	24 ± 5	25 ± 6
Weight, kg	76 ± 15	75 ± 16
Height, cm	173 ± 10	174 ± 9
Sex	12/2	8/1
End-tidal P_{CO_2}, mmHg		
Sea level	39 ± 3	39 ± 2
Normobaric hypoxia	36 ± 2	36 ± 2
Peak O_2 uptake, ml·kg^{-1}·min^{-1}	46 ± 8	48 ± 6
Sea-level time-trial performance, min	75 ± 13	73 ± 8

Values are means ± SD.

long × 2.3 m high clear vinyl-sided, portable hypoxia rooms (Colorado Altitude Training, Boulder, CO). One room was always maintained at SL conditions (sham: P_B ~756, O_2 = 20.9%), while the ambient O_2 concentration of the other room was progressively reduced by ~0.30% O_2 [or increased by 150 m equivalents (equiv)] on consecutive nights from ~16.2% O_2 (2,200 m equiv) on *night 1* to ~14.4% O_2 (3,100 m eq) on *night 7*. CO_2 scrubber units maintained a low concentration of CO_2 (0.04–0.10%) within each room on all nights. The environmental conditions for the hypoxia rooms were stabilized before the volunteers reported each night. All volunteers remained in their room until 0530 each morning. Thus all volunteers remained in their respective environmental condition for a total of 7.5 h each night.

Between the two adjacent hypoxia rooms was a staff member, who each night monitored and controlled the ambient conditions of the hypoxia rooms. The tubing, wires, vents, fans, and sensors were presented and visually oriented such that the volunteers were unaware of O_2 level differences within the rooms.

In the morning after *night 7* of sleep, resting measurements were obtained at SL outside the hypoxia rooms. The volunteers were blinded to all data displays. Then the volunteers were driven to a local airport and flown to Colorado Springs, CO (2,100 m, P_B ~600 mmHg) to stay overnight in an apartment under staff supervision. The staff in Colorado Springs was blinded to the volunteers' sleep treatment until the entire study was completed. From 0600 to 0700 on the next morning, the volunteers were driven from the apartment to the summit of Pikes Peak for the 5-day HH phase.

Sleep Monitoring

Relative activity during sleep for 2 nights during the SL baseline phase, 7 nights during the treatment phase, and 4 nights during the HH exposure phase was quantitated for each volunteer by a small motion detector worn on one wrist, as previously described (16). Briefly, sleep/awake duration and number of awakenings were determined by motion analysis (Motion Logger with Action 4 software, version 1.13, Ambulatory Monitoring, Ardsley, NY). During sleep, on the other wrist, volunteers also wore a small pulse oximeter (model 3100, Nonin, Plymouth, MN) that had an adhesive finger sensor for recording of Sa_{O_2}, heart rate (HR), and the number of desaturation events (>6% drop from baseline for ≥8 s). To avoid possible variability in device sensitivity, volunteers were assigned the same motion detector and oximeter throughout the study.

Ventilatory measures. Resting ventilation was determined at SL, after 1 h during NH conditions equivalent to 4,300 m (P_{O_2} = 93 mmHg), at SL in the morning after the last night of sleep treatment, and on *days 1, 2, 3*, and *5* during HH residence. All resting ventilation tests, as well as pulse oximetry, were done with the volunteers awake, fasting, and rested for ≥30 min. During these procedures, the volunteers were in a seated position while connected to a breathing circuit by a rubber mouthpiece and nose clip and to a finger pulse oximeter unit (model 8600, Nonin) for recording of resting Sa_{O_2} and HR. All procedures were performed using a breath-by-breath gas analyzer and metabolic measurement system (Vmax 229, Sensormedics, Yorba Linda, CA). The mean $P_{ET_{CO_2}}$ obtained over the last 10–15 min of each of the resting ventilation test sessions was the primary variable used to assess VEacc.

Acute Mountain Sickness

AMS was assessed *1*) twice during SL baseline (morning and afternoon), each evening at 2200 just before the volunteers entered the hypoxia rooms and then each morning at 0530 h before they left the hypoxia room; *2*) at 2,100 m just prior to ascending Pikes Peak (0530); and *3*) while living at Pikes Peak, four times each on *days 1–4* [0700 (i.e., <1 h after awakening), 1400, 1700, and 2000] and twice on *day 5* (0700 and 1400). The prevalence and severity of AMS were determined from information gathered using a shortened version of the Environmental Symptoms Questionnaire (ESQ) (6). The ESQ was administered using a personal digital assistant (model iPAQ, Hewlett-Packard). A weighted average of scores from 11 symptoms (e.g., headache, lightheadedness, dizziness), designated "AMS-C," was calculated. AMS-C scores ≥0.7 indicated the presence of AMS. For each day at HH, the AMS-C score obtained at 0700 and the peak AMS-C score obtained after 0700 were used in the analyses. Prevalence was defined as the percentage of individuals in each group who were sick (i.e., AMS-C score ≥0.7) at 0700 and after 0700.

At the completion of each AMS assessment, Sa_{O_2} was measured for 1 min by finger pulse oximetry (Voyager Pulse Oximeter, Dolphin Medical, Hawthorne, CA). The mean Sa_{O_2} was therefore matched in real time to each AMS assessment.

Peak O_2 uptake. One peak O_2 uptake ($\dot{V}O_{2peak}$) test was conducted during the USARIEM baseline phase at SL. An incremental, progressive exercise bout to volitional exhaustion on a motor-driven treadmill (model 9.15HR, Smooth Fitness, King of Prussia, PA) was used to assess $\dot{V}O_{2peak}$. Measurements of O_2 uptake ($\dot{V}O_2$) for each of the 2-min stages were obtained using a metabolic cart (True Max 2400, Parvo Medics, Sandy, UT). Volunteers walked for a total of 10 min (5 stages) starting at 3 METS (4.8 m/h and 0% grade) and ending at 8 METS (6.4 m/h and 7% grade). The treadmill speed and grade were then changed so that the volunteers would run at 9.7 m/h and 0% (10 METS), respectively. Then, for every 2-min stage thereafter, the speed and/or grade were changed, such that each successive power output increased by ~1 MET (or 3.5 $ml \cdot min^{-1} \cdot kg^{-1}$). The test continued until $\dot{V}O_2$ failed to increase or the volunteer could not continue.

Treadmill Endurance Assessments

Endurance was determined using a treadmill (model 9.15HR, Smooth Fitness) twice during the USARIEM baseline SL phase and three times during HH residence (*days 1, 2*, and *5*). The first assessment at SL was used for practice to familiarize the volunteers to the procedures. All treadmill endurance assessments included 5 min of walking at 4.8 m/h and 0% grade for warm-up followed by 20 min of steady-state exercise at a power output equal to 45 ± 5% of SL $\dot{V}O_{2peak}$. During steady-state exercise, the speed was maintained at 5.6 m/h and the grade was raised as appropriate (if necessary). For each volunteer, the same speed and grade were used for all steady-state assessments at SL and during HH residence. During the last 5–10 min of each 20-min steady-state exercise session, $\dot{V}O_2$ was measured using a metabolic cart (True Max 2400, Parvo Medics). The volunteers were then allowed 5 min to stretch, use the bathroom, etc.

The volunteers then completed 11.3 km as fast as possible (treadmill TT). While the grade remained at 3%, the volunteers could alter the speed to walk or run at any time for any duration during the TT. Volunteers were continuously informed of the distance, but not the time, elapsed. This type of TT performance test has high test-retest reproducibility and low coefficient of variance and has been used similarly at altitude (11, 15). Between-group changes in TT duration were the primary means to assess whether NH treatment minimized the decrement in exercise performance during HH residence.

Other Measures Associated With Exercise Tests

During all exercise tests, HR was monitored continuously with a HR watch (Polar Electro, Woodbury, NY), Sa_{O_2} was monitored via noninvasive finger pulse oximetry (model 8600, Nonin), and ratings of perceived exertion [RPE, 6–20 on the Borg scale (8)] were determined at the end of every workload (during $\dot{V}O_{2peak}$) or every 5 min (during the endurance tests).

Venous Blood Samples

While the volunteers were seated just prior to exercise at SL and on the mornings (~0800 to 0900) of *days 1, 2*, and *5* during HH

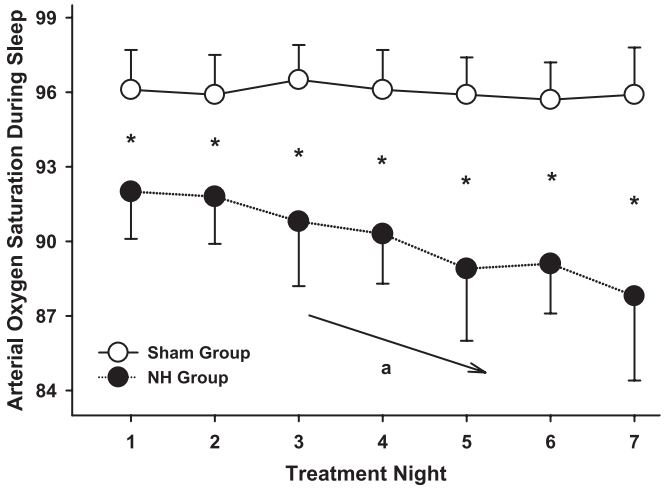

Fig. 2. Sa_{O_2} during NH and sham treatment. For the sham group, Sa_{O_2} remained at ~96% for the entire 7 days of treatment. Sa_{O_2} for the NH group began at ~92% and progressively fell over the 7 nights to ~88% ($^aP < 0.01$). For each of the 7 nights, Sa_{O_2} for the NH group was lower ($*P < 0.01$) than for the sham group.

residence, 2-ml resting venous blood samples were taken from an arm vein for determination of Hb concentration and hematocrit (Hct) using an i-STAT portable clinical analyzer (Abbott Point of Care, Princeton, NJ). At SL and in the mornings on *day 2* (i.e., ~25 h after arrival) and *day 5* in HH, additional 13-ml resting venous blood samples were obtained for analysis of erythropoietin (EPO; Quantikine IVD ELISA, R & D Systems, Minneapolis, MN), epinephrine and norepinephine (HPLC; Bio-Rad), and cortisol and aldosterone (enzyme immunoassay; ALPCO Diagnostics, Salem, NH).

Statistical Analyses

Data were analyzed using commercial software (Statistica, version 7.1, Statsoft, Tulsa, OK). Two factor (group × time) ANOVAs with repeated measures on one factor (time) were performed on dependent variables (e.g., $P_{ET_{CO_2}}$, Sa_{O_2}) that related directly or indirectly to the main hypothesis. In all cases, when significant main effects or interactions were found, Newman-Keuls post hoc test was applied. Recent studies of similar experimental procedures using unacclimatized SL volunteers were consulted to determine appropriate sample sizes for the major hypothesis related to changes in $P_{ET_{CO_2}}$, AMS symptomatology, and exercise performance (3, 12, 23). It was assumed that sham treatment would have no effect on $P_{ET_{CO_2}}$ and that the magnitude of changes in $P_{ET_{CO_2}}$ induced by NH treatment would be similar to that induced by HH treatment of a similar cohort of six volunteers (2). In that study at 4,300 m (2, 3), $P_{ET_{CO_2}}$ was reduced by an average of 3.6 ± 2.1 mmHg, AMS was nearly eliminated, and exercise performance was greatly improved by HH treatment. With the assumption that NH treatment would similarly reduce $P_{ET_{CO_2}}$ at 4,300 m, a minimum of eight volunteers in each group were required for detection of a statistically significant between-group difference ($\alpha < 0.05$, $\beta < 0.20$). Daily differences between groups for AMS prevalence during HH residence were analyzed using χ^2 test for independent groups. Values are means ± SD. $P \leq 0.05$ was considered statistically significant for all analyses.

RESULTS

Before Hypobaric Exposure

Sleep monitoring during treatment. Each night during sleep treatment, Sa_{O_2} was lower ($P < 0.01$) for the NH group than for the sham group, with the nightly difference between groups becoming progressively larger from *night 1* to *night 7* as the ambient O_2 concentrations for the NH group progressively decreased (Fig. 2). HR did not differ between groups for any night and was maintained at 64 ± 7 beats/min over the 7 nights. For each of the 7 nights, both groups experienced identical rates of awakenings (1 ± 1 per night) and similar percentage of being asleep while they were supine (94 ± 5%), with no change among nights. Also for all nights, the sham group did not experience any desaturation events. For *nights 1* and *2*, the number of desaturation events (<3 per hour) for the NH group did not differ from their SL baseline or from the sham group. However, beginning on *night 3* (4 ± 4 desaturation events/h) and continuing through *night 7* (33 ± 33 desaturation events/h), the number of desaturation events progressively increased for the NH group ($P < 0.01$) and also differed ($P < 0.01$) from the sham group. Lastly, not one volunteer in either group reported AMS on any night during the entire sleep-treatment period.

In the morning after *night 7* of sham or NH treatment, each volunteer was asked privately if they thought they slept under SL or NH conditions for the 7 nights. Of the nine volunteers who slept under sham conditions, four were correct and five "had no idea." Of the 14 volunteers who slept under NH conditions, 4 were correct, 3 were incorrect, and 7 "had no idea."

Ventilatory measures before and immediately after sleep treatment. Table 2 shows resting ventilatory assessments for both groups measured during the SL baseline phase, during the acute NH exposure to 4,300 m equiv (~1 h), and in the morning at SL within 2 h after awakening from *night 7* of the sleep-treatment session. Prior to sleep treatment, there were no differences between groups in any of the measures at SL or

Table 2. *Resting ventilatory measures before and after sleep treatment*

	SL Baseline		Acute NH		PostTreat, SL	
	Sham	NH	Sham	NH	Sham	NH
Ventilation, l/min btps	8.9 ± 2	8.5 ± 1	9.8 ± 1	10.0 ± 2*	8.8 ± 1†	8.7 ± 2†
O_2 uptake, ml/min	311 ± 73	296 ± 35	377 ± 78*	392 ± 74*	291 ± 61†	281 ± 53†
CO_2 output, ml/min	234 ± 59	242 ± 32	251 ± 60	266 ± 51*	243 ± 58	228 ± 42†
End-tidal Po_2, mmHg	101 ± 5	103 ± 6	49 ± 4*	49 ± 3*	104 ± 4†	106 ± 4†
End-tidal Pco_2, mmHg	39.1 ± 1.9	39.1 ± 3.0	36.1 ± 1.7*	36.2 ± 2.3*	38.3 ± 3.0	34.9 ± 2.6*†‡
Arterial O_2 saturation, %	97 ± 1	97 ± 1	81 ± 3*	81 ± 5*	97 ± 1†	97 ± 1†
HR, beats/min	62 ± 9	64 ± 9	72 ± 12	72 ± 7*	64 ± 9	70 ± 10

Values are means ± SD. Acute, <1 h of exposure to 4,300 m equivalent; PostTreat, SL, <2 h after awakening after *night 7* of sleep treatment, measured at sea level (SL); Sham, sham control group; NH, normobaric hypoxia group. $*P < 0.05$ vs. within-group SL baseline. $†P < 0.05$ vs. acute NH. $‡P < 0.01$ vs. PostTreat, SL sham.

during the <1-h exposure to NH. Moreover, in general, all values were similarly changed for both groups from SL baseline to acute NH ($P < 0.05$). At the postsleep treatment at SL, all values were nearly identical to their corresponding values measured during SL baseline, except for a $P_{ET_{CO_2}}$ for the NH group ($P < 0.01$). $P_{ET_{CO_2}}$ for the NH group also was lower than their acute NH $P_{ET_{CO_2}}$ ($P < 0.05$) and than the sham group during the posttreatment measurement ($P < 0.01$). The lower within- and between-group $P_{ET_{CO_2}}$ for the NH group indicates that VEacc was successfully induced by the nightly NH treatments.

Travel days. The volunteers were awakened at ~0530 on the day of travel to Colorado. After the resting ventilatory assessments, volunteers showered, ate breakfast, and were driven to Logan Airport (Boston, MA). Depending on availability, flights departed between 0900 and 1400 (median 1200) and arrived in Colorado between 1130 and 1630 (median 1430). The volunteers were then driven to a local apartment (2,100 m altitude), where they stayed until ~0600 the next morning, when they were driven in ~1 h to the Pikes Peak Laboratory at 4,300 m.

An interval of ~25 h occurred between the time the volunteers stepped out of the hypoxia rooms in Natick, MA, and their arrival at Pikes Peak. Within this interval, the volunteers were exposed to ~21 h of moderate HH conditions (~2,100 m) that included ~5 h of air travel and ~16 h of living in the apartment in Colorado Springs. Just prior to departure from the apartment, resting Sa_{O_2} for both groups was similar (~95 ± 3%), resting HR was lower for the NH group than for the sham group (66 ± 10 vs. 77 beats/min, $P < 0.05$), and not one volunteer in either group reported AMS at 2,100 m.

Exposure to High Altitude (HH)

Resting ventilation. The between-group difference in resting $P_{ET_{CO_2}}$ at SL posttreatment ($P < 0.01$) was no longer detectable during HH residence (Fig. 3). Resting $P_{ET_{CO_2}}$ for both groups declined from *day 1* to *day 2* (from ~33 to 31 mmHg, $P < 0.01$) before leveling off at ~30 mmHg on *days 3* and *5*. There also were no differences between groups during HH residence on any day for resting ventilation ($\dot{V}_E$), $\dot{V}_{O_2}$, CO_2 output, end-tidal P_{O_2}, and HR. Sa_{O_2} measured concomitantly with resting $\dot{V}_E$ increased ($P < 0.01$) from acute NH (81 ± 4%) and *days 1* and *2* during HH residence (82 ± 4%) to *day 5* during HH residence (85 ± 5%), but there was no difference between groups on any of the days.

Daytime resting Sa_{O_2}. The Sa_{O_2} data that were independently obtained in conjunction with the ESQ were consistent with the Sa_{O_2} values collected as part of the resting ventilation assessment. That is, Sa_{O_2} increased ($P < 0.01$) for both groups during HH residence from 82 ± 4% on *days 1* and *2* to 85 ± 5% on *day 5*, with no differences between groups on any of the days during HH residence.

Sleep monitoring in HH. In contrast to a lack of difference in Sa_{O_2} between groups while awake during HH residence, the mean sleep Sa_{O_2} was higher for the NH group than for the sham group for the entire sojourn (80 ± 4 vs. 76 ± 4%, $P < 0.05$), with nightly between-group differences ranging from 2% to 6% (Fig. 4). The NH group also tended to awaken fewer times than the sham group (12 ± 6 vs. 17 ± 7 per night, $P = 0.06$).

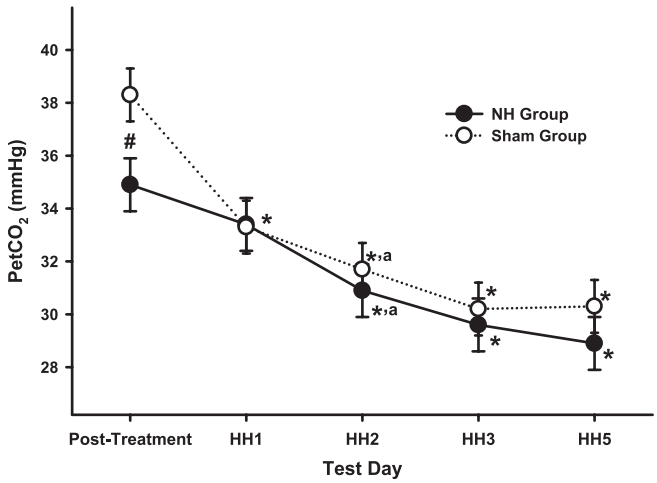

Fig. 3. Ventilatory acclimatization after treatment at SL and Pikes Peak. There were no between-group differences in resting end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) for any of the test days on the summit of Pikes Peak, even though there was a large difference ~25 h earlier, just after treatment at SL (#$P < 0.01$). On *morning 1* of hypobaric hypoxia (HH1), $P_{ET_{CO_2}}$ had decreased for both groups to a similar value of ~33 mmHg, with $P_{ET_{CO_2}}$ falling more for the sham group (*$P < 0.01$) than for the NH group ($P = 0.08$). On HH2, $P_{ET_{CO_2}}$ continued to fall similarly from HH1 for both groups ($^aP < 0.01$), with $P_{ET_{CO_2}}$ for each group being lower than their respective posttreatment values (*$P < 0.01$). $P_{ET_{CO_2}}$ did not decline further from HH2 to HH3 or HH5 for either group.

However, there were no other clear distinctions between groups for all the other variables measured or calculated during sleep (i.e., HR, number of desaturation events, or duration of wakefulness).

From *night 1* to *night 4* of sleep during HH residence, for both groups combined, there were declines ($P < 0.05$) in HR (from 80 ± 10 to 74 ± 7 beats/min), number of desaturation events (from 333 ± 381 to 201 ± 233 per hour), and number of nightly awakenings (from 17 ± 9 to 11 ± 5) and increases ($P < 0.05$) in sleep Sa_{O_2} (from 76 ± 5 to 81 ± 4%) and percent time asleep (from 76 ± 18 to 84 ± 14%).

Daytime AMS. On *day 1*, ~80% of the volunteers in each group reported AMS. On *day 2*, AMS prevalence fell to 29% for the NH group but only to 67% for the sham group ($P < 0.01$). For each of the remaining 3 days, AMS prevalence for both groups became similar. The mean AMS-C score was highest for both groups during *day 1* but then fell rapidly to or below the AMS-C score of 0.70 for each of the remaining 4 days for both groups ($P < 0.01$). There were no significant differences between groups for any of the days for AMS-C scores during the HH exposure.

AMS just after awakening. Figure 5 shows that the prevalence of AMS upon awakening was more than twice as high for the sham group as for the NH group during *mornings 1* and *2* at HH ($P < 0.01$). For *mornings 3* and *4*, the prevalence of AMS fell sharply for the sham group but remained 8% and 21% higher ($P < 0.01$) than for the NH group. During HH residence, the mean overall AMS-C score upon awakening was higher for the sham group than for the NH group (0.83 ± 0.14 vs. 0.34 ± 0.12, $P < 0.02$). Moreover, only the sham group's mean AMS-C score exceeded the AMS-C score of 0.70 while under HH conditions (*mornings 1* and *2*).

Exercise assessments. Table 3 shows the responses of $\dot{V}_E$, $\dot{V}_{O_2}$, HR, Sa_{O_2}, and RPE to the identical, individually deter-

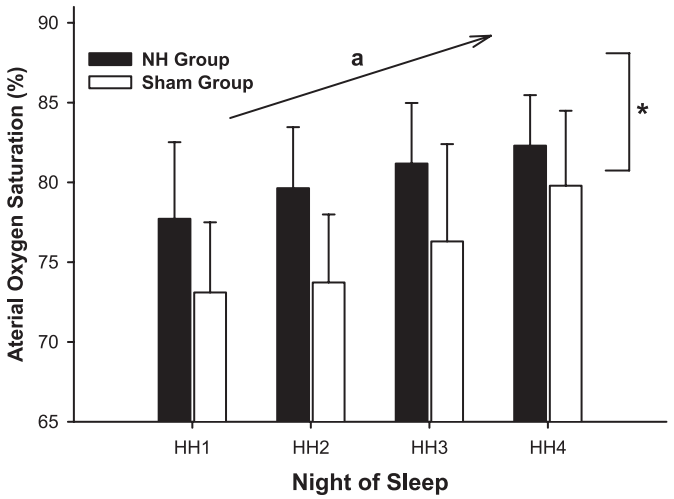

Fig. 4. Sa_{O_2} during sleep under HH conditions. During sleep for the entire 4 nights under HH conditions, mean Sa_{O_2} was higher for the NH group than for the sham group (80 ± 4 vs. 76 ± 4%, *$P < 0.05$). For both groups, Sa_{O_2} progressively increased from *night 1* to *night 4* (from 76 ± 5% to 81 ± 4%, [a]$P < 0.05$).

mined treadmill speed and grade at SL and during *days 1*, *2*, and *5* of HH residence. Except for a higher RPE score for the sham group than for the NH group during *day 1* of HH, all responses between groups did not differ among the test days. For both groups, from SL to each day during HH, $\dot{V}_E$ and HR were higher, while Sa_{O_2} was lower ($P < 0.05$). For both groups from *day 1* to *day 5* during HH, $\dot{V}_E$ and Sa_{O_2} were higher ($P < 0.05$), while $\dot{V}_{O_2}$ did not change and did not differ between groups.

TT exercise performance. TT performance, along with HR, Sa_{O_2}, and RPE, at SL and during HH residence are shown in Table 4. There were no differences between groups for any measure at SL or on any of the 3 test days during HH, except RPE was higher for the sham group on *day 1* of HH ($P < 0.05$). HR and Sa_{O_2} were reduced and TT performance time increased from SL to each day during HH ($P < 0.05$). In both groups, TT performance was significantly improved on *day 5* of HH compared with *days 1* and *2* of HH ($P < 0.05$).

Blood measures. At SL, there were no differences between groups in any of the preexercise resting blood values. In addition, on any day during HH, there were no differences between groups for Hb concentration or Hct. However, Hb concentration and Hct were higher on each day during HH than at SL ($P < 0.01$).

EPO for both groups increased ($P < 0.01$) from SL to *day 2* of HH. On *day 2*, EPO was lower ($P < 0.01$) for the NH group than for the sham group. Then from *day 2* to *day 5* during HH, EPO declined ($P < 0.01$) for both groups and no longer differed from the SL values. However, while under HH conditions, EPO levels remained lower for the NH group than for the sham group ($P < 0.02$).

There were no changes from SL to HH for epinephrine or aldosterone, nor were there any differences between groups on any of the test days. Norepinephrine and cortisol increased ($P < 0.01$) from SL to *day 5* during HH, but there were no differences between groups.

DISCUSSION

This study tested the hypothesis that VEacc induced by NH treatment would be evident under HH conditions at an altitude of 4,300 m and would, in turn, ameliorate AMS symptoms and benefit TT exercise performance. However, there was little indication that VEacc induced by NH sleep treatment was retained during wakefulness in HH, and there were no differences relative to the sham group for AMS (when assessed >1 h after awakening) or exercise performance outcomes during the 5 days of residence at 4,300 m. In contrast, VEacc was clearly and consistently expressed (via elevated Sa_{O_2}) during sleep in HH and may have contributed to the reduction in AMS and to the attenuated EPO response observed shortly after awakening in HH.

Induction of VEacc has been reported previously during repeated daily exposures to HH or NH treatment (17, 18, 20, 22). Acquisition and retention of VEacc resulting from the repeated HH treatment appears to be an important response associated with reduced AMS symptoms and improved TT performance during subsequent exposure to 4,300 m (2–4). In contrast, a significant improvement in Sa_{O_2} induced over 1 wk of 3-h daily NH treatment exposures was evident only when measured in NH conditions, but not when assessed during HH residence at 4,300 m, and there was also no improvement in TT performance (5). The lack of any retained ventilatory or TT performance benefit during HH residence after NH treatment was considered to be due to a loss of VEacc resulting from the nontreatment time intervals being too long or the NH treatment either not inducing sufficient VEacc or simply not being beneficial during subsequent HH residence (5, 27). On the basis of this information, there was an expectation for the

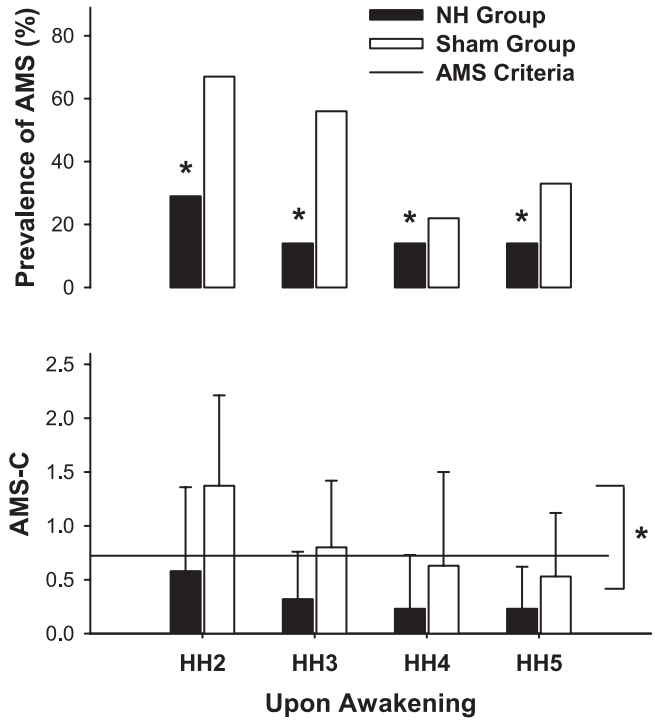

Fig. 5. Symptoms of AMS upon awakening under HH conditions. A much larger proportion of volunteers were sick in the sham group than the NH group just after awakening throughout HH. There was an overall difference (*$P < 0.02$) between groups for AMS prevalence and severity (AMS-C score).

Table 3. *Responses during steady-state exercise at SL and HH*

	SL		HH					
			Day 1		*Day 2*		*Day 5*	
	Sham	NH	Sham	NH	Sham	NH	Sham	NH
Resting ventilation, l/min btps	37 ± 9	37 ± 7	45 ± 9*	45 ± 11*	43 ± 9*	48 ± 7*	49 ± 9*†	51 ± 11*†
O_2 uptake, ml/min	1,582 ± 351	1,573 ± 307	1,604 ± 321	1,595 ± 277	1,497 ± 324	1,652 ± 378	1,566 ± 372	1,588 ± 318
HR, beats/min	129 ± 18	124 ± 7	140 ± 15*	138 ± 7*	138 ± 15*	138 ± 11*	132 ± 12*	134 ± 15*
Arterial O_2 saturation, %	97 ± 1	97 ± 1	74 ± 3*	75 ± 4*	73 ± 6*	75 ± 4*	76 ± 9*†	78 ± 4*†
RPE	8 ± 1	8 ± 1	11 ± 3‡	9 ± 1	11 ± 3	10 ± 4	11 ± 3	10 ± 4

Values are means ± SD. HH, hypobaric hypoxia; RPE, rating of perceived exertion. *$P < 0.01$ vs. SL. †$P < 0.05$ vs. HH *day 1*. ‡$P < 0.05$ vs. HH *day 1* NH.

present study that, by using a shorter time interval between the final NH treatment and HH residence, as well as by using a NH treatment that was 2.5–3.8 times as long as previous NH treatment studies (5, 27) and over twice as long as a highly successful HH treatment (4), VEacc would be retained, AMS would be reduced, and TT performance would be improved during subsequent HH residence.

We were therefore surprised in the present study that, after successful induction of a large VEacc (i.e., −4 mmHg $P_{ET_{CO_2}}$), there were no differences between groups for resting or steady-state exercise ventilatory measures, AMS symptoms (when assessed >1 h after awakening), or TT performance beginning within a few hours after ascent to 4,300 m. The paucity of differences between groups during most of each day during wakefulness, as well as the clear difference in Sa_{O_2} during sleep, at 4,300 m was likely not due to controllable, potentially confounding experimental factors for at least a few reasons. *1*) The similarities between groups during the baseline period in age, weight, height, resting SL and NH $P_{ET_{CO_2}}$ values, venous blood values, $V_{O_{2peak}}$, and TT performance duration prior to sleep treatment minimized the possibility that there would be non-treatment-related differences in ventilatory or exercise responses during HH residence. *2*) Sa_{O_2} was monitored during sham and NH sleep to ensure that the groups were always exposed to and receiving significantly different treatments for each of the 7 nights. The sleep oximeters used during the treatments were later used by the same volunteers during HH residence to eliminate possible differences in signal variability between devices. Moreover, Sa_{O_2} data were collected independently using different brands of oximeters among the multiple resting and exercise daytime assessments throughout each day to facilitate intrinsic data comparison and result validation. *3*) Objective measures indicated that significant VEacc was successfully induced by NH treatment and remained after the completion of treatment and on the day of travel. *4*) To eliminate possible treatment bias, all volunteers and staff at Pikes Peak were blind to the treatment received by each volunteer and to the results of all ventilatory, TT performance, and hematological assessments until the entire study was completed.

Because of these experimental considerations, we are confident in stating that VEacc induced by NH sleep treatment is expressed primarily during sleep, but not wakefulness, during HH residence. Over the 4 nights at 4,300 m, not only were the sleep Sa_{O_2} levels significantly higher for the NH group, but there was also a tendency ($P = 0.06$) for the NH group to awaken less than the sham group. Moreover, the higher sleep Sa_{O_2} observed for the NH group likely contributed to their lower AMS-C scores (≤1 h after awakening) and the reduced resting blood EPO levels (<3 h after awakening) relative to the sham group during HH residence. Previous studies reporting a direct relationship between higher Sa_{O_2} levels and either reduced AMS (1, 3) or blood EPO levels (13, 19) or between lower Sa_{O_2} levels and increased AMS (9) are consistent with our interpretation. Whether our findings of apparent sleep response specificity may be related to possible physiological differences or signaling mechanisms in response to NH and HH treatments (10, 25) that may be of benefit for the planning of future acclimatization strategies cannot be determined from the results of this study.

The daytime resting or exercise absolute values and responses from SL to the initial assessments during HH residence, as well as for the observed rate of acclimatization over the 5 days at 4,300 m, for $P_{ET_{CO_2}}$, Sa_{O_2}, HR, AMS (other than when just awakened), catecholamines, and fluid and stress hormones were similar for both groups. All the values, responses, and rates of change also were within an expected normal range relative to previous studies that used similar groups of unacclimatized SL residents who did not undergo treatment before or while living under HH conditions (2, 4, 11, 12, 21, 23, 24, 26, 28). Collectively, these results indicate that

Table 4. *Responses during time-trial performance assessments at SL and HH*

	SL		HH					
			Day 1		*Day 2*		*Day 5*	
	Sham	NH	Sham	NH	Sham	NH	Sham	NH
HR, beats/min	172 ± 15	165 ± 11	148 ± 18*	152 ± 15*	153 ± 21*	151 ± 19*	149 ± 24*	153 ± 15*
Arterial O_2 saturation, %	96 ± 1	97 ± 1	72 ± 6*	74 ± 4*	72 ± 6*	74 ± 7*	73 ± 6*	77 ± 4*
RPE	13 ± 2	13 ± 2	15 ± 3‡	14 ± 4	15 ± 3	15 ± 4	15 ± 3	13 ± 4
Time, min	75 ± 13	73 ± 8	106 ± 21*	103 ± 19*	103 ± 21*	106 ± 22*	99 ± 18*†	95 ± 15*†

Values are means ± SD. Time, time to complete 11.3-m time trial. *$P < 0.01$ vs. SL. †$P < 0.05$ vs. HH *days 1* and *2*. ‡$P < 0.05$ vs. HH *day 1* NH.

there is little justification for using NH treatment prior to HH residence.

Resting $P_{ET_{CO_2}}$ is typically reported to be lower (2, 3, 23, 24) when unacclimatized SL residents are rapidly exposed to HH (e.g., 4,300 m, P_{O_2} ~93 mmHg). In the present study, it was therefore not unexpected that $P_{ET_{CO_2}}$ fell similarly from SL baseline by ~3 mmHg for both groups prior to any experimental treatment in response to the lower ambient P_{O_2} associated with acute NH conditions (also ~93 mmHg). The ~6-mmHg fall in $P_{ET_{CO_2}}$ for the sham group from SL baseline to *day 1* during HH residence also was anticipated on the basis of previous resting ventilatory data collected from 37 men (24) who were SL residents and similarly rapidly exposed to the identical altitude of 4,300 m. We also anticipated that the reduction in $P_{ET_{CO_2}}$ during initial HH exposure would be greater than that observed during acute NH conditions for the same P_{O_2} of ~93 mmHg on the basis of emerging evidence suggesting ventilatory response differences between NH and HH exposures at the same ambient P_{O_2} (10).

What was not expected was our finding that the $P_{ET_{CO_2}}$ of the NH group did not remain lower than that of the sham group on any of the 5 days during HH residence. Previously we showed that a ~4-mmHg reduction in $P_{ET_{CO_2}}$ (i.e., the same $P_{ET_{CO_2}}$ reduction observed in the present study) for SL residents undergoing 4-h daily HH treatments was retained 24 h later during subsequent HH residence at 4,300 m (446 mmHg, P_{O_2} = 93 mmHg) (2). In another study (24), $P_{ET_{CO_2}}$ also was ~4 mmHg lower for moderate-altitude residents (living at 1,600 m) than for SL residents assessed at their respective baseline elevations. When the SL and moderate-altitude residents were later assessed while living at 4,300 m, $P_{ET_{CO_2}}$ remained ~4 mmHg lower each day for the first 5 days for the moderate-altitude residents than for the SL residents. The implication for the present study is that if NH treatment was to be as effective as HH treatment during HH residence, the induced ~4-mmHg lower $P_{ET_{CO_2}}$ of the NH group than the sham group should have been similarly retained during HH residence. Why there was no evidence of initial or retained difference for $P_{ET_{CO_2}}$ between the NH and sham treatment groups during HH residence remains to be determined.

Collectively, in light of our results, experimental design considerations, and at least one study (17) that reported that VEacc induced by NH treatment remained evident for up to 1 mo (but only when assessed under NH conditions), a likely and seemingly unavoidable interpretation for a lack of difference between groups for nearly all measures is that NH sleep treatment, potent enough to have induced significant VEacc, simply did not provide any additional ventilatory, AMS symptom, or exercise performance benefit while the volunteers were awake during HH residence. In contrast, a significantly higher mean sleep Sa_{O_2} in the NH than in the sham group during HH residence may have contributed to less awakening during sleep and significantly attenuated AMS NH symptoms and EPO response soon after awakening. Further studies are needed to determine the mechanisms responsible as to why, during subsequent HH residence, *1*) NH treatment is not nearly as effective as HH treatment and *2*) physiological responses and outcomes resulting from the NH sleep treatment are specific to sleep.

Perspectives and Significance

This study clearly shows that NH treatment relative to sham treatment provides little useful benefit during subsequent HH residence. It should be emphasized that the lack of effectiveness of NH treatment was not likely related to an inadequate stimulus or response, since the magnitude of the ventilatory acclimatization induced by NH treatment was comparable to that of previous similar studies using HH treatment. In addition, the time interval between the end of NH and later HH residence in the present study was deliberately comparable to that of previous HH treatment-to-HH residence studies. Yet only HH treatment reduced AMS and improved exercise performance during HH conditions. Interestingly, NH treatment does provide significant AMS and exercise benefits when the outcome measures are assessed under NH conditions. The most important conclusion resulting from the sum of all this information is that NH and HH treatments clearly cannot be used interchangeably and are not as effective as preacclimatization strategies to reduce AMS and improve exercise performance during subsequent HH residence.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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